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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/073,272	02/13/2002	Richard J. Wurtman	215055.01401	6824

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PATENT ADMINISTRATOR  
KATTEN MUCHIN ZAVIS ROSENMAN  
525 WEST MONROE STREET  
SUITE 1600  
CHICAGO, IL 60661-3693

[REDACTED] EXAMINER

JONES, DWAYNE C

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 05/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	10/073,272	WURTMAN ET AL.
	<b>Examiner</b>	<b>Art Unit</b>
	Dwayne C Jones	1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on \_\_\_\_\_.
- 2a) This action is FINAL.      2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.
- 4) Claim(s) 1-17 is/are pending in the application.
  - 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1-17 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.
 

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.
 

If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
  - a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                  | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>5</u> . | 6) <input type="checkbox"/> Other: _____.                                   |

## DETAILED ACTION

### ***Status of Claims***

1. Claims 1-17 are pending.
2. Claims 1-17 are rejected.

### ***Information Disclosure Statement***

3. The information disclosure statement filed on September 5, 2002 has been reviewed and considered, see enclosed copy of PTO FORM 1449.

### ***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 7-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of a memory impairment or cognitive dysfunction, does not reasonably provide enablement for the treatment of Alzheimer's disease as well as the prevention of memory impairment or cognitive dysfunction, including, Alzheimer's disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re

Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The instant invention is directed to the treatment of Alzheimer's disease as well as the prevention of memory impairment or cognitive dysfunction. The method comprises administering citicoline.

(2) The state of the prior art

The compounds of the inventions are citicoline. However, the prior art does not teach that these citicoline compounds possess the property of prevention of memory impairment or cognitive dysfunction, including, Alzheimer's disease, (see Weiss, G). In addition, there is also evidence of the extreme difficulty and unpredictability in the treatment of Alzheimer's disease. In fact, there are a wide variety of therapeutic strategies for treating Alzheimer's disease that are being pursued. The major categories of these strategies are collected in Table 1 of Patel (see page 82).

## (3) The relative skill of those in the art

The relative skill of those in the art of pharmaceuticals is high.

## (4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. Supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5<sup>th</sup> Cir. 1978); In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24 (CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5 (BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art); In re Wright, 999 F.2d 1557, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or

pharmaceutical activity of citicoline prior to filing of the instant invention was an unpredictable art.

(5) The breadth of the claims

The instant claims are very broad. For instance, claims 7, 8, 11, 13, 15 and 17 are directed to the prevention of memory impairment or cognitive dysfunction, including, Alzheimer's disease plethora of compounds of citicoline. The breadth of claims was a factor in Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d (Fed. Cir.), cert. Denied, 502 U.S. 856 (1991). In the Amgen case, the patent claims were directed to DNA sequences that encoded amino acid sequences. Because a very small change in the amino acid sequence of a protein can result in a very large change in the structure-function activity of a protein and because the laws of protein folding are in such a primitive state, predicting protein structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for a date in the future.

(6) The amount of direction or guidance presented

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fischer, 427 F.2d 839, 166 USPQ 24; Ex Parte

Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575. In the instant case, given the unpredictability of the physiological or pharmaceutical activity of a citicoline to be effective in the prevention of memory impairment or cognitive dysfunction, including, Alzheimer's disease is insufficient for enablement. The specification provides no guidance, in the way of enablement for citicoline other than the an example where the administration of citicoline was given to a rat where certain cognitive tests were performed. In addition, the specification does not provide any enablement of citicoline that could be employed in this invention other than for the treatment of a memory impairment or cognitive dysfunction. The specification provides no guidance, in the way written description for prevention of memory impairment or cognitive dysfunction, including, Alzheimer's disease. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient

number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity.

See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

(7) The presence or absence of working examples

As stated above, the specification discloses the use of citicoline for as the prevention of memory impairment or cognitive dysfunction, including, Alzheimer's disease. However, the instant specification only has enablement for as the treatment of memory impairment or cognitive dysfunction, including, Alzheimer's disease, with the administration of citicoline.

(8) The quantity of experimentation necessary

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to

the direction in which the experimentation should proceed.” In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue “painstaking experimentation study” to determine how the administration of citicoline is effective in the prevention of memory impairment or cognitive dysfunction, including, Alzheimer’s disease that would be enabled in this specification.

***Claim Rejections - 35 USC § 102***

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 1 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Weiss, G. Weiss, G. teach of the administration of citicoline to treat a variety of diseases such as Alzheimer’s disease as well as conditions related to decreased learning and memory, (see abstract).

8. Claims 1-7, 11, 12 and 17 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Bradley et al. of U.S. Patent No. 5,977,174. Bradley et al. teach that it is known in the art that citicholine and CDP-choline are neuroprotective agents, which can be used to treat neurodegenerative disorders involving loss of cognition, *inter alia* Alzheimer’s disease. In addition, Bradley et al. teach that it is known in the art that fatty

acids, such as docosahexaenoic acid. Bradley et al. also teach of the pharmaceutical compositions of neuroprotective agents along with pharmaceutically acceptable excipients and carriers, (see columns 5 and 8) as well as modes of administration, including sustained-release formulations (see column 9).

***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss, G. Weiss, G. teach of the administration of citicoline to treat a variety of diseases such as Alzheimer's disease as well as conditions related to decreased learning and memory. Weiss, G. also disclose of the citicoline metabolites of cytidine and choline, (see abstract). Weiss, G. is silent to period of administration of at least six weeks to the individuals in need thereof. However, the determination of a dosage having the optimum therapeutic index is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug. Hence, the reference makes obvious the instant invention.

13. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bradley et al. of U.S. Patent No. 5,977,174. Bradley et al. teach that it is known in the art that citicholine and CDP-choline are neuroprotective agents, which can be used to treat neurodegenerative disorders involving loss of cognition, inter alia Alzheimer's disease. In addition, Bradley et al. teach that it is known in the art that fatty acids, such as docosahexaenoic acid. Bradley et al. also teach of the pharmaceutical compositions of neuroprotective agents along with pharmaceutically acceptable excipients and carriers, (see columns 5 and 8) as well as modes of administration, including sustained-release formulations (see column 9). Von Borstel of US Patent Publication 2001/0005719, which possesses a priority date of August 31, 1998. Von Borstel disclose of administering a pyrimidine nucleotide precursor in order to effectively treat

inter alia, neurodegenerative disorders, namely Alzheimer's disease, (see pages 8a and 9). In fact, Von Borstel teach of the administration of the pyrimidine nucleotide precursors of cytidine and uridine, (see page 3). Von Borstel teach of pharmaceutical compositions of these compounds, (see page 5). "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Accordingly, it would have been obvious to one having ordinary skill in the art to combine these prior art references because they are shown to be effective for treating the very same ailment.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (703) 308-4634. The examiner can normally be reached on Mondays through Fridays from 8:30 am to 6:00 pm. The examiner can also be reached on alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Art Unit: 1614

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-

1235.

DWAYNE C. JONES  
PRIMARY EXAMINER

Tech. Ctr. 1614

May 12, 2003